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Natural Medicinal Compounds from Marine Fungi towards Drug Discovery: A Review

Parthiban Brindha Devi and Ridhanya Jayaseelan

Abstract

Marine fungi are species of fungi which live in estuaries environment and marine environment. These species are found in common habitat. Marine fungi are rich in antimicrobial compounds such as anthrones, cephalosporins, peptides, steroids. These compounds which are derived mainly focused in the area of anti-inflammatory, anti-oxidant, anti-fungal, anti-microbial, anti-fouling activity. Bioactive terpene compounds are produced by marine fungi and marine derived fungi can produce sclerotides, trichoderins. Marine fungi have become the richest sources of biologically active metabolites and structurally novel in the marine environment. In a recent study the marine derived fungi *dichotomomyces cejpai* exhibits activity towards cannabinoid which is used to treat alzheimer dementia. *Aspergillus unguis* showed significant acetyl cholinesterase besides its anti-oxidant activity. These acts as a promising intent for discovery of pharmaceutically important metabolites like alkaloids, peptides. Computational (in silico) strategies have been developed and broadly applied to pharmacology advancement and testing. This review summarizes the bioactive compounds derived from marine fungi in accordance with the sources and their biological activities.

Keywords: marine fungi, bioactive compounds, docking, metabolites

1. Introduction

To date there are about 100,000 fungal species, it is expected about one million species that are to be present. In spite of the fact that assessments for the quantity of fungi around 1.5 to more than 5 million, likely less than 10% of fungi have been identified till date. Marine derived fungi are rich in new metabolites [1, 2]. Marine derived fungi consists of secondary metabolites which acts a promising pharmacological and biological properties [3]. Fungi are significant parasites of nutrient cyclers and primary producers. These are tremendously understudied in the marine domain and information on their function is obliged by the fungal dispersion and drivers on worldwide scales [4]. Marine fungi are significant source of secondary metabolites. Despite the fact that marine parasites are less investigated in contrast, various valuable hits have been acquired from the drug discovery point of view adding to their significance in the product discovery [5, 6]. Source of drugs isolated from fungi are being used as camptothecin, torreyanic corrosive, vincristine and cytarabine and paclitaxel. Drug resistance towards diseases like tuberculosis, cancer

and HIV-AIDS have been biological target with restricted accomplishment [7]. A few classes of particular metabolites from marine fungi have a wide scope of bio activities against various activities. From marine fungi, more than thousand metabolites have been accounted which can be possibly developed as drugs [8–10]. The source of these marine fungi metabolites is differed as their natural surroundings have been accounted from different sources, for example, algae, sponge, fungi and mangrove derived fungi from bottom residue [11]. Fungi can also be harnessed as sources of chemicals, food and biofuels when people exploit metabolism of fungi [12]. Secondary metabolites are produced by fungi for different purposes, including threat of different pathogens, iron chelation and microorganisms. These metabolites have been recognized from EDF [13]. Isolation of fungi from marine samples has regularly led to the recuperation of microorganisms, which are morphologically, trophically and ecologically like fungi yet are false organisms [14]. Fungi are generally conveyed in marine conditions from intense ocean to polar ice covers. They are found in a wide range of dead and living organic matter. Fungi have been made with those related with sediments, with explicit substrates like algae, driftwood, corals and specifically with sponges [15]. Reliably, fungi confined from sponges represent the biggest number (28%) of novel compounds revealed from marine fungi [16]. In spite of the fact that bio activities of secondary metabolites from marine fungi unveil clinical targets; they are not well constituted for pipelines of drugs and none of them right now is available [17]. To date, in excess of 180 bioactive secondary metabolites got from deep ocean fungi have been reported. These natural metabolites obtained are generally organic and compounds like Pencillium, Polyketides is largely discovered. These incorporate compounds with antimicrobial, anticancer, antiprotozoal, antifungal and antiviral activities [18]. Indeed, even in deep aqueous biological systems, an unsuspected high assorted variety of fungal species was discovered utilizing molecular approaches. At first samples are collected from the ocean. The next step is fungal cultures and sample preparation. In the lab, sterility was acquired by vertical laminar flow hood and bunsen burner. Cultures were allowed to grow aerobically at 25°C with atmospheric pressure and ambient temperature. GYPS medium is used for the growth of strains (1 g glucose, 1 g peptone, 1 g starch 1 g yeast and 30 g ocean salts). Then it is freeze-dried at 80°C. DNA is extracted by homogenizing each sample with sterile glass dabs at 30 rpm. DNA was removed from developed strains with a Fast DNA Spin pack. In Cloning and sequencing, the SSU rRNA qualities were amplified utilizing PCR (primers). Transfer DNA was amplified by PCR at 94°C for 1.30 minutes including 37 cycles of 94°C for 30 s, followed by 48°C for 1.25 min, and 72°C for 1.5 min. The PCR amplification with a last extension step and performed at 72°C for 10 min. The fragments were refined with a High Pure PCR kit (Roche) furthermore, were cloned in the DH5 equipped cells and pGEM-T vector. The two strands was determined utilizing Sequencher 4.6 (GeneCodes), A different grouping arrangement was developed for every phylum utilizing Clustal X 1.81 containing all the databases. After this protocol, 1733 sequences from Basidiomycota,, 4117 sequences from Ascomycota, 215 sequences from Chytridiomycota, 621 sequences from Glomeromycota and 292 sequences from Zygomycota is obtained from various branches of phylogenetic fungal species. Every phylum was then exposed to a numerous grouping arrangement methodology, trailed by neighbor-joining method. Phylogenetic trees were envisioned by utilizing Treeview. The phylogenetic neighbors nearest to the ecological sequence were chosen, and afterward phylogenetic analysis were performed. A different sequence arrangement methodology was performed utilizing CLUSTALX 1.81, and the arrangement was refined by eye. After these evaluation, phylotypes were indicated utilizing a cutoff of 98% (pairwise distance). Then qPCR analysis

were performed with 10- μ l blends utilizing iQ SYBR green Supermix (Bio-Rad), which contained SYBR green PCR buffer, 2.7 μ M dATP, 2.7 μ M dGTP, 2.7 μ M dCTP, 2.7 μ M dTTP, and 0.42 U of iTaq DNA polymerase (Bio-Rad). At that point 0.35 μ M preliminary MH2 (5'TTCGATGGTAGGATAG3') and 0.35 μ M primer FungqPCR1 (5'TGTCGGGATTGGGTAATTT3') were added to the blend. Reactions were carried out in optical tubes and were fixed with microseal film. All reactions performed with Chromo 4 thermocycler, utilizing an underlying denaturation at 94°C for 3 min to initiate the compound, trailed by 35 or 40 cycles of denaturation at 94°C for 30 s and furthermore expansion at 48°C for 45 s and afterward by plate perusing. The dissociation curve for temperatures from 65–95°C was estimated after the last qPCR cycle. All informations analyzed utilizing Opticon Monitor 3. Samples which showed the most grounded signals in two starter runs were compared at in a last run. Different plasmid concentrations were utilized to build a standard curve for supreme quantification. Using this formula, standards are found: molecules/ μ l = $a / (\text{plasmid length} \times 660) \times (6.022 \times 10^{23})$ where a is the plasmid of concentration in (μ g/ μ l), 6.022 $\times 10^{23}$ -molar constant, 660- average molecular weight of one base pair [19]. The greater part of the work on secondary metabolites of marine organisms has concentrated on genera, mainly *Penicillium*, *Aspergillus* and additionally *Fusarium* and *Cladosporium*, moreover the less contemplated species merit extraordinary consideration [20]. Biological activity can also be identified using In Silico methods. It gives fast predictions for a large set of compounds in a high-throughput mode. The aim of target discovery is the validation and identification of suitable drug targets for therapeutic intervention and discovery of novel chemical molecules that acts on the most relevant targets for a disease under study. In silico methods include quantitative structure–activity relationships, databases, similarity searching, homology models, pharmacophores, and other molecular modeling, data mining, machine learning, data analysis and network analysis tools that use a computer. Such methods have seen frequent use in the discovery and optimization of physicochemical characterization [21, 22].

2. Secondary metabolites and bioactive compounds

Two new metabolites, *carbonarones* A (1) and B (2), were acquired from the marine-fungi *Aspergillus carbonarius* detached from the marine residue gathered at Weizhou island of China. It indicated moderate cytotoxicity against K562 cells with IC50 estimations of 56.0 and 27.8 μ g/ml, individually [23]. 14-norpseurotin A, 29-nordammarane triterpenoid 6 β show noteworthy antimicrobial activity against *Bacillus subtilis*, *Escherichia coli* and *Micrococcus lysolei* with MICs of 3.74, 14.97 μ M [24]. From the fungi extracts *Ascochyta heteromorpha*, the agent of a foliar infection of oleander (*Nertum oleander*), another cytochalasin named ascochalasin was separated together with deoxaphomin and cytochalasins A and B. Cytochalasins are an enormous gathering of contagious metabolites created by a few genera of fungi which demonstrated diverse biological activities. These compound binds to actin filaments and block the polymerization and also involved in the elongation of actin [25–28]. Three new metabolites, microsphaeropsone A–C (1–3) with an interesting oxepino[2,3-b]chromen-6-one, were detached from the endophytic growth *Microsphaeropsis species* [29] (**Figure 1**).

A semisynthetic dihydrooxepino[2,3-b]chromen-6-one 7 was set up by oxidation of the allylic alcohol 1 with manganese dioxide [29]. Marine-derived fungi *Aspergillus versicolor* MF160003 for the pharmacologically dynamic secondary metabolites prompts the disclosure of another Xanthenone derivative, 3-hydroxy

pinselin, with five known compounds, pinselin, methyl 8-hydroxy-6-methyl-9-oxo-9H-xanthene-1-carboxylate, 2-methoxy pinselin, aspergillusone A 12-O-acetyl-AGI-B4 [30]. Screening for new bioactive metabolites from the marine-determined variety of *Aspergillus*, an *Aspergillus versicolor* DJ013 separated from a coastal, Dongji Island, China. EtOAc separate resulted in identification and isolation of new furandione compounds, named asperfurandiones A and B [31]. Botryosphaerin were detached from the endophytic fungi *Botryosphaeria* sp. MHF associated with *Maytenus hookeri*. A compound CJ-14445 showed inhibition towards *Saccharomyces cerevisiae*, *Candida albicans* and *Penicillium avellaneum* UC-4376 in correlation with nystatin which was utilized as a positive control [32] (Figure 2).

2.1 Bioactivities

Xanalteric acids I (38) and II (39) are the two new compounds which were segregated from the organism *Alternaria* sp., taken from leaves of the Mangrove plant *Sonneratiaceae*, gathered in Dong Zhai Gang Mangrove Garden on Hainan Island, China. Compounds 38 and 39 showed frail anti-microbial action against multidrug-resistant *S. aureus* with MIC estimations of 686.81–343.40 μ M [34]. *Spicellum roseum* yielded the equivalent *trichothecene* as is delivered by the *Trichothecium roseum*. The compound demonstrated antimicrobial properties against specific yeasts of *Saccharomyces cerevisiae* and *Candida albicans* [35]. The absolute number of lignin from chosen white, soft and brown rot fungi were isolated. These outcomes have uncovered that, most elevated ligninolytic capacity was seen in *P. ostreatus*, *P. eryngii* *S. hirsutum* (white rot fungi), *C. puteana* *H. pinastri* (brown

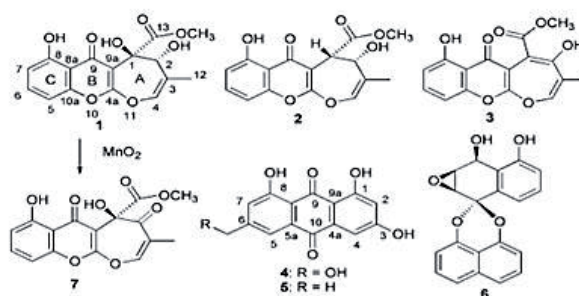


Figure 1.

Compounds 1–6 isolated from the endophytic fungus *Microsphaeropsis* sp. and 7 obtained by the oxidation of 1 [29].

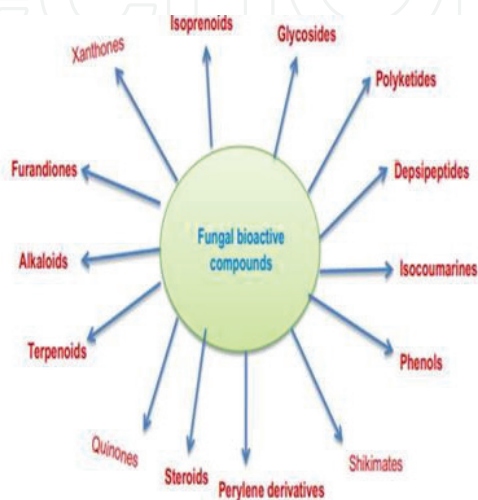


Figure 2.

Different types of fungal metabolites [33].

rot fungi) *F. oxysporum* and *B. dothidea* (soft rot fungi) [36]. The fungi recognized as *Neopestalotiopsis* sp., active against *D. phaseolorum*. The outcomes feature that the endophytes are equipped for delivering compounds that might be utilized to control plant pathogens. The compound fumiquinone B is accounted for just because as an antifungal operator against *D. phaseolorum*, a significant plant pathogen around the world. This is additionally the first report of the production of fumiquinone B by the *Neopestalotiopsis* [37]. Fungi *M. albus* identified with *Cinnamomum zeylanicum*, recognized five classes of unstable compounds like alcohols, esters ketones, lipids and acids which smothered the action of pathogenic fungi, namely *Pythium ultimum*, *Phytophthora cinnamomi* *Rhizoctonia solani*, *Ustilago hordei*, *A.fumigates*, *Stagnosporanodorum*, *Sclerotinia sclerotiorum*, *Tapesia yallundae*, *F. solani*, *Cercospora beticola*, *C. albicans* and *Verticillium dahlia* [38]. The detached metabolite sclerotiorin from *Cephalotheca faveolata* had the capacity to incite apoptosis in malignant growth cells.

Sclerotiorin had apoptotic properties for colon malignant growth (HCT-116) cells by means of BAX and inactivated the BCL-2 proteins and further degrade the caspase-3 catalyst advancing apoptosis in dangerous cells [39]. Antibacterial action of the detached bioactive parts from endophytic growth *Phomopsis* sp. inside *Plumeria acutifolia* against the bacterial pathogens *E. coli*, *Klebsilla* sp *Pseudomonas* sp., *S. aureus*, *B. subtilis* also, *S. typhi* and it had no huge impact on *C. albicans* [40, 41]. *Awajanoran*, another dihydrobenzofuran derivative, was separated from an agar-culture of *Acremonium* sp. AWA16–1, which had been separated from ocean mud gathered at Awajishima Island in Japan. This compound restrained the development of A549 cells, the human lung adenocarcinoma cell line, with an IC50 estimation of 17 µg/ml, and furthermore demonstrated antimicrobial action [42]. R-135853 against different contagious strains and furthermore shows the MICs of R-135853 for the strains utilized in vivo. R-135853 showed strong activity against *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. neoformans* and *C. guilliermondii* with MICs varying from 0.016 to 0.5 g/ml [43].

3. Docking studies

A chain of 1-(1H-1,2,4-triazol-1-yl)- 2-(2,4-difluorophenyl)- 3-subbed 2-propanols (5a–5y) which are analogs of fluconazole, have been structured and integrated by means of Cu(I)- catalyzed azide–alkyne cycloaddition based on computational docking investigations to the dynamic site of the cytochrome P450 14α-demethylase

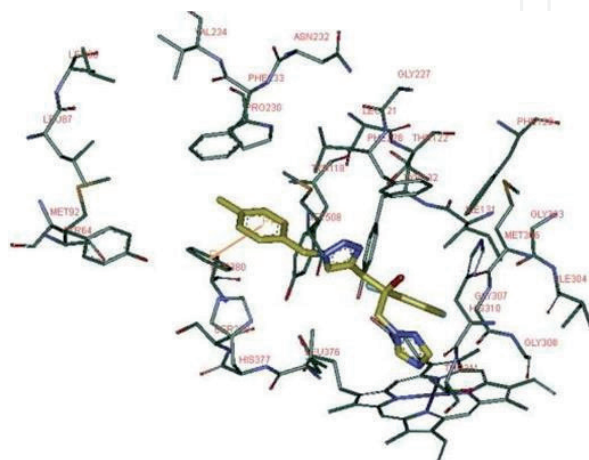


Figure 3.
 Compounds binding geometry of the new inhibitor 5 l in the active site of CYP5l [44].

(CYP51). Target compounds were assessed against eight human pathogenic fungi in vitro. Compound 5 l demonstrated the best antifungal activity [44] (**Figure 3**).

Tyrosol, extracted from *P. chrysogenum* DXY-1, a marine fungi utilized as a QS inhibitor against *C. violaceum* and *P. aeruginosa*. The docking results show that tyrosol hinders the QS system of CviR in *C. violaceum* by binding to the DNA-binding domain and blocking the gene expression of pathogens [45] (**Figure 4**).

Three compounds (heptadecanoic acid, 16 methyl-, methyl ester; 9,12-octadecadienoic acid; cis-9-octadecenoic corrosive) identified and were screened against the skin cancer protein (Hsp90) by in-silico docking. The metabolites in two fungal strains of Hypocrea species were analyzed in GC-MS and the compound (Heptadecanoic corrosive, 16 methyl) indicated the best outcome against skin cancer protein [46] (**Figure 5**).

A 3D model of the cytochrome P450 14a-sterol demethylase of *C. albicans* (CA-CYP51) was built on the premise of the sequence homology with structure of the cytochrome P450 14a-sterol demethylases of *M. tuberculosis* (MT-CYP51). The model of CA-CYP51 was utilized to clarify the antifungal movement of a chain of 1,4-benzothiazine and 1,4-benzoxazine imidazole derivatives. All compounds receive comparable binding modes inside the catalytic site of CA-CYP51. These outcomes will be used to address the structure and synthesis of new strong antifungal compounds supplied with hostile to Candida action [47] (**Figure 6**).

Mannich bases of thiosemicarbazide is tested for anti-fungal activity. Docking of compounds was performed on the pdb structure of Lanosterol 14 α -demethylase (CYP51A1, P45014DM) utilizing Vlife MDS 3.5 as target. All incorporated atoms

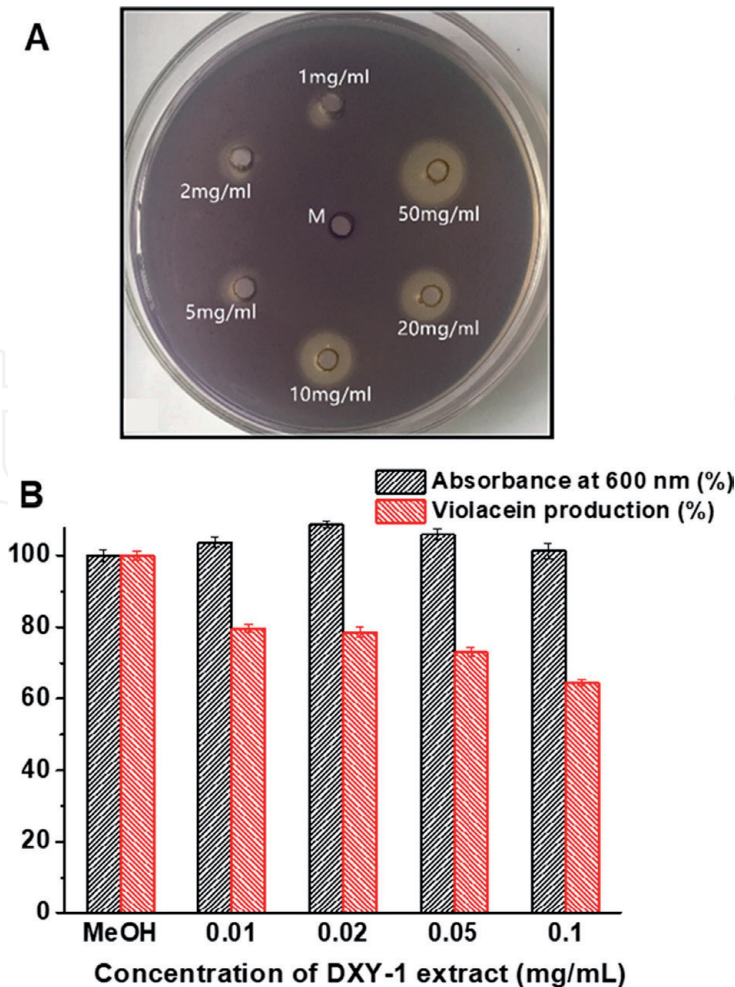


Figure 4.
Effects of tyrosol on the growth of *C. violaceum* CV026 and violacein production in *C. violaceum* [45].

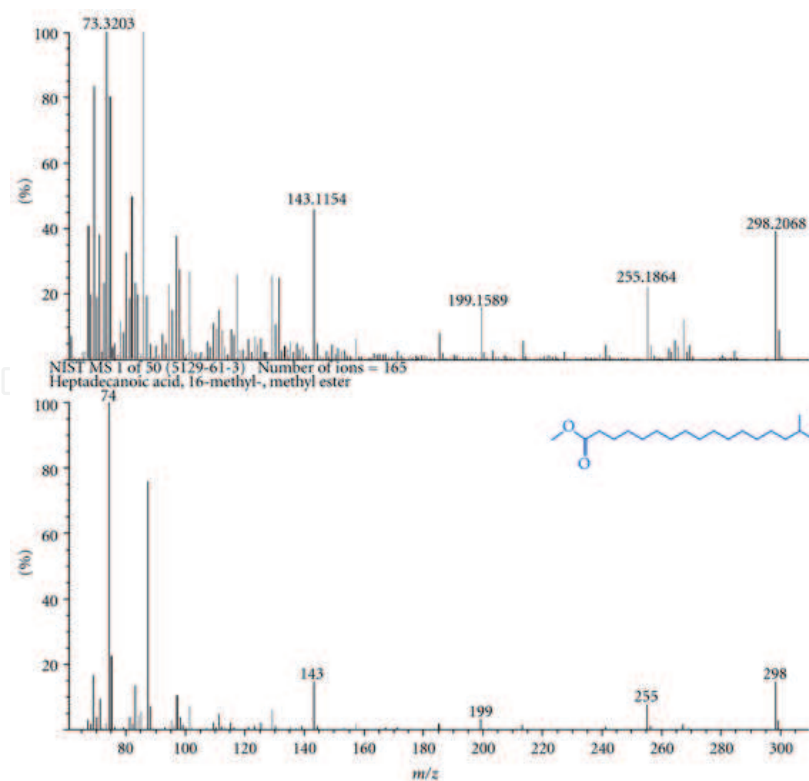


Figure 5.
GC-MS result of potential compound Heptadecanoic acid, 16 methyl derived from *Hypocrea lixii* TSK8 [46].

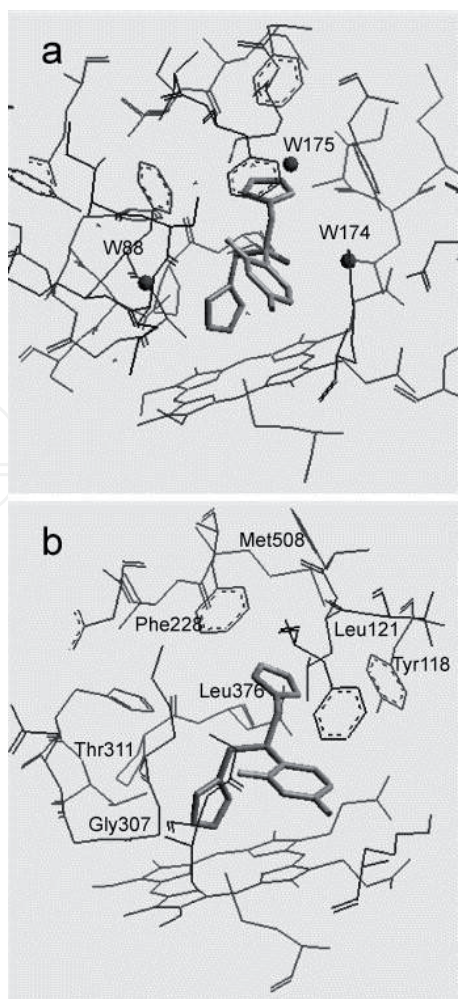


Figure 6.
Best docking solution of fluconazole into the catalytic site of CA-CYP51 [47].

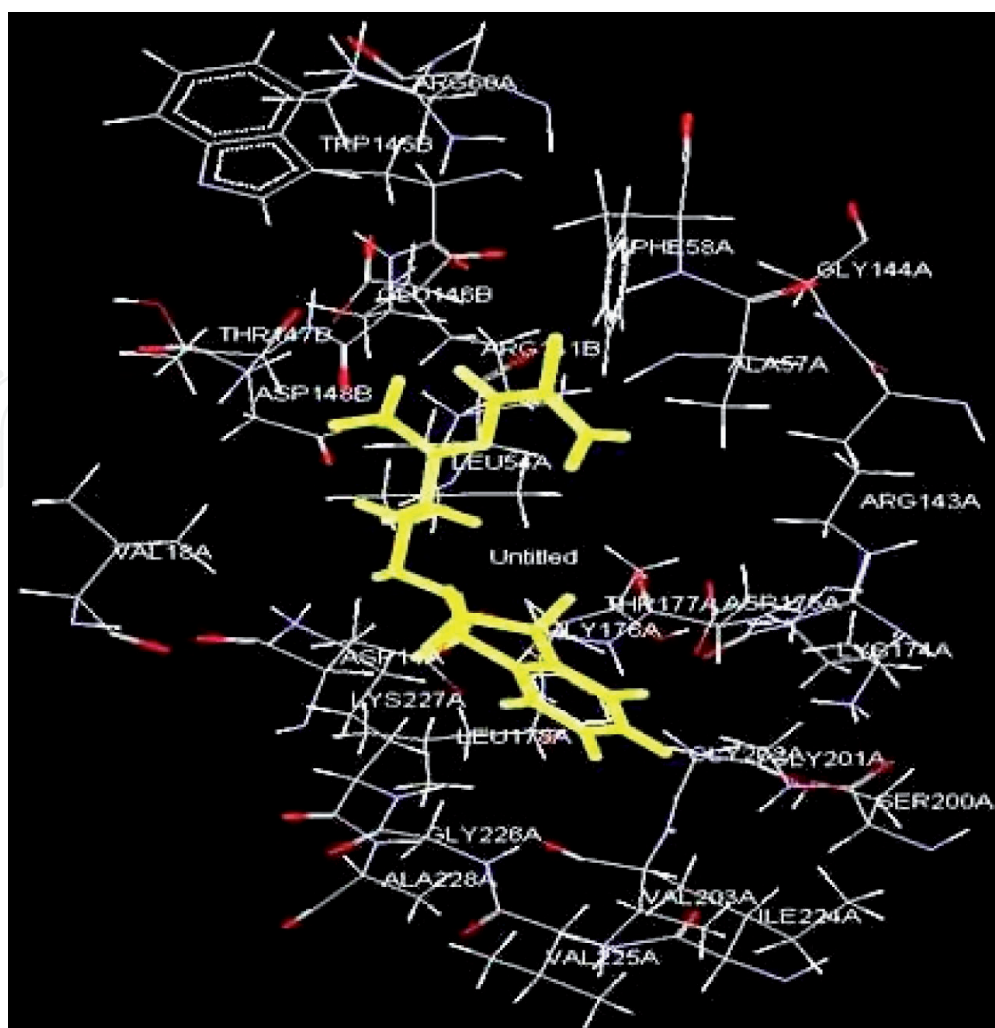


Figure 7.
Representative interactions shown by K_{20} with amino acid residues of CYP51A1, P45014DM [48].

were docked into a similar binding site. Docking study demonstrated a solid hydrophobicity between amino acids, such as Arginine (ARG141), Glutamine (GLU146), with hydrogen of aldehyde at 2.279. The amino acids included are Glycine GLY176A, Aspartine ASP175A, Threonine THR147B Lysine LYS227A, Phenyl alanine PHE58A and Arginine ARG141B which may be assuming a significant role in the specific binding of compounds with target [48] (**Figure 7**).

4. Recent discoveries

In this investigation, researchers scanned for new secondary metabolites from ocean inferred growth strain FKJ-0025 and found two new compounds, sarcopodinols A (1) and B (2), together with a known compound, SF-227. This is the principal report of secondary metabolites separated from family Sarcopodium. Cytotoxicity test utilizing human tumor cell lines, 1 demonstrated cytotoxicity against Jurkat cells. Eminently, 2 demonstrated cytotoxicity against HL-60, Jurkat, and Panc1 cells. These outcomes recommend that the absence of 5'-OH is the significant factor behind the lethality against HL-60 and Panc1 cells [49]. The novel Anthraquinone, 2-(dimethoxymethyl)-1-hydroxyanthracene-9,10-dione, jointly with nine studied compounds (2–10), were taken from a marine derived fungi *A. versicolor*. 1 showed solid inhibitory activity against MRSA ATCC 43300 and MRSA CGMCC 12409 (with MIC estimations of 3.9 and 7.8 $\mu\text{g/mL}$ separately) and moderate activity against analyzed strains of *Vibrio*. Molecular docking studies with

AmpC β -lactamase IV and topoisomerase indicated least binding interactions and supported antimicrobial movement of this compound is a novel compound merited expanding consideration as a source of antibacterial factor [50].

4.1 Antimicrobial agents

Antifungal peptides created by certain lactic acid bacteria strains have high potential for applications in expansive scope of nourishments. The component of peptides antifungal movement is identified with their properties, for example, low atomic weight, secondary structure, concentrations. The antifungal peptides were proposed to be utilized as bio-additives to decrease as well as supplant chemical preservatives [51]. White rot fungi that go under the division eumycota are heterogeneous gathering of fungi having ability to degrade a wide assortment of difficult compounds. Xenobiotic degradation may be due to non-specific enzymes. Manganese peroxidase, laccase, lignin peroxidase were explored seriously for the wide scope of xenobiotics. These organisms are having the ability to separate the lignin in wood without degrading cellulose, sometimes both cellulose and lignin will be degraded [52]. Nanotechnology for the creation of nanoparticles utilizing fungal cells is an ongoing phenomenon. Parasite like *Colletotrichum sp.*, *A. clavatus*, and *Pestalotia sp.* have been utilized for improvement of nanoparticles against pathogenic microorganisms [33].

5. Conclusion

Bioinformatics has built up itself as a basic apparatus in target revelation. In silico pharmacology paradigm is progressing and presents a rich exhibit of chances that will help with expediting the revelation of new targets, and leads to discovery of compounds with biological activities. The drug design is based on analysis of structure of fungal species complexes. Various evaluations are found using quasi in vivo assay and pharmacokinetic analysis. For example, X-ray structures of *C. albicans* CYP51 complexes with posaconazole and VT-1161, providing a molecular mechanism for the potencies of these drugs against pathogens that are intrinsically resistant to fluconazole.

Future perspectives

Comparative structural analysis indicates the phylum-specific CYP51 features highlights that could coordinate future rational improvement of more productive expansive range antifungals. Basic assay normally focused on antimicrobial and antifungal activity. Viable and safe medications in the field on infections and malignant growth are unquestionably required. Subsequently, it is recommended to widen biological screens for the once in a while examined biological activities, which might be significant for the treatment of ceaseless illnesses.

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